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The Application of Ultra-High-Frequency Ultrasound in Dermatology and Wound Management

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Abstract

The management of lower extremity wounds is frequently performed by means of clinical examination, representing a challenge for the clinician due to the various conditions that can potentially enter differential diagnosis. Several diagnostic techniques are available in the dermatologist's arsenal as a support to diagnosis confirmation, including dermoscopy and ultrasonography. Recently, a novel ultrasonographic technique involving the use of ultra-high ultrasound frequencies has entered the scene, and appears a promising tool in the diagnostic workup of skin ulcerative lesions. The focus of this review is to discuss the potential role of ultra-high-frequency ultrasonography in the diagnostic workup of wounds in the light of the current applications of the technique.

Keywords

diagnosis, clinical signs and symptoms score, duplex ultrasonography, ABI, ABPI

Ultrasonography in Dermatology: An Historical Overview

Ultrasonography (US) is a widely used, noninvasive, real-time diagnostic technique that finds application in several medical branches. The operating principle of US is based on the reflection of sound waves when encountering different tissues.[1-4] In particular, the degree of reflection of the ultrasound waves depends on the acoustic impedance of the tissue, which is the result of tissue density and beam's angle of incidence.[2] When at the interface between 2 different tissues a large difference in impedance is present, the acoustic energy can be either reflected or scattered depending on the beam's angle, while a reduced difference in impedance allows the majority of the sound waves to be transmitted deeper in the tissue.[1,3] The acoustic impedance also determines the characteristic echo pattern of a tissue, which is of great importance when performing diagnosis on US images. On the basis of the echo pattern, a tissue can be defined as anechoic, hypoechoic, or hyperechoic depending on the type of signal produced.[2,3]

The choice of the frequency to be employed depends on the clinical query. In fact, there is an inverse proportionality between the US frequency and wavelength, which results in a different degree of penetration in the tissues. Lower US frequencies are therefore characterized by a higher depth of penetration of the US wave, at the expense of image resolution. On the other hand, higher US frequencies provide better image resolution, but limited depth of penetration.[4]

Moreover, the possibility to evaluate blood flow through Doppler US appears extremely relevant when assessing the degree of vascularity of a tissue.[2,3]

US has been employed as a diagnostic support in dermatology since the late 1970s, when it was first introduced by Alexander and Miller for the evaluation of skin thickness.[5] Its unique characteristics in terms of versatility, reduced invasiveness, and repeatability with high diagnostic value made US a valuable tool in supporting clinical diagnosis in dermatology.[4] At present, US is employed for the assessment of skin lesions of various etiology, both for diagnostic and therapeutic purposeses.[2,6]

In dermatology, the need for high-resolution imaging of superficial anatomical structures of reduced dimensions has favored the application of US frequencies >15 MHz. Recently, the introduction of ultra-high ultrasound frequencies (>30 MHz) for the diagnosis of skin lesions has

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Table 1. UHFUS Features.

UHFUS frequency	70 MHz	48 MHz
Bandwidth	29-71 MHz	20-46 MHz
Axial resolution	30.0 µm	50.0 µm
Lateral resolution	65.0 µm	110.0 µm
Maximum depth	10.0 mm	23.5 mm
Image width (maximum)	9.7 mm	15.4 mm
Image depth (maximum)	10.0 mm	23.5 mm
Focal depth	5.0 mm	9.0 mm

Abbreviation: UHFUS, ultra-high-frequency ultrasound.

responded to the previously unmet need for a submillimeter resolution imaging of small anatomy and superficial tissue layers.[7] This review evaluates the current literature available on the applications of ultra-high-frequency ultrasound (UHFUS) in the diagnostic workup of skin lesions.

Ultra-High-Frequency Ultrasound: What Is New

UHFUS is defined as an ultrasonographic technique involving the use of ultrasound frequencies higher than 30 MHz, which allow to obtain submillimeter resolution of superficial anatomical structures.[7]

UHFUS was developed in the mid-1990s in the preclinical setting, where it found application for the study of tumor biology, pharmacokinetics of drugs, and several pathologic conditions in small animals. In particular, UHFUS allowed to monitor tumor growth in animal models and their changes after antineoplastic therapy, to visualize the microvascularization of neoplastic masses, and to study the progression of atherosclerotic lesions and the medium-intimate thickness of the arterial wall in murine models.[8-11] Moreover, the technique appeared extremely valuable as it provided an accuracy comparable with bioptic sampling.[12] In the early 2000s, UHFUS was introduced in the clinical setting, where it is employed in various medical branches. As axial resolution proportionally increases with ultrasound frequency, the use of ultra-high frequencies provides submillimeter image resolution, although the shorter wavelength limits the depth of penetration of the ultrasound beam. From this perspective, UHFUS appears suitable for the investigation of small structures located within the first centimeters from the surface of application of the probe. For example, the use of 70 MHz frequencies allows to obtain 30-µm resolution of structures located within 10.0 mm from the surface (Table 1).[7] Therefore, the improved degree of visualization of superficial anatomical structures has favored the diffusion of UHFUS in all the fields where the detailed investigation of small anatomy is required.

To date, more than 60 clinical studies have been published on the dermatological, vascular, musculoskeletal, intraoral, and small parts applications of UHFUS.[7]

A Review of Current UHFUS Applications in Dermatology

In total, 22 studies[13-34] were retrieved from the literature on the applications of UHFUS in dermatology (Table 2). The articles included report both on normal anatomy and skin diseases. An overview on the evaluation of normal anatomy of skin and annexes and of benign and malignant skin lesions is reported.

The Study of Normal Anatomy

Five studies in total reported on the investigation of normal anatomy by means of UHFUS.[13,14,23,25,30]

The first study describing normal anatomy on UHFUS was the one by Liffers et al,[13] which described normal skin in comparison with the appearance of a malignant melanoma. A double image acquisition by means of UHFUS and high-resolution magnetic resonance imaging was performed, and revealed a superiority of UHFUS in imaging superficial microstructures, such as hair follicles and sweat glands, although the imaging depth was lower compared with magnetic resonance imaging. Two studies investigated the structure of the nails.[14,23] Berritto et al[23] described the nail plate as a double hyperechoic band corresponding to the superficial and ventral nail plates and a hypoechoic layer in between corresponding to the middle nail plate. Beneath the nail plate, the nail bed is represented as a hypoechoic layer. Vogt et al[14] compared the skin and nail structure as imaged by means of UHFUS and optical coherence tomography (OCT). Although spatial resolution was significantly higher for OCT, UHFUS presented a wider field of view and greater imaging depth. The authors concluded that despite the higher resolution provided by OCT, UHFUS allowed to image both skin and subcutaneous tissue. In a study by Wortsman et al,[25] the UHFUS characteristics of skin annexes were described. The hair follicles and hair tracts appeared as oblique hypoechoic bands located in the dermis and contacting the upper hypodermis, and the arrector pili muscles emerged from the hair follicle region as oblique hypoechoic structures reaching the upper dermis. The oval hyperechoic structures attached to the hair follicles were described as the sebaceous and Montgomery glands. The apocrine glands appeared as round or oval hypo- or anechoic structures in the axillary, perineal, perianal, and inner aspects of the proximal parts of the arms and thighs.[25]

Firooz et al[30] reported on the variations in skin thickness depending on gender and age. According to their results, epidermal and dermal thickness decreased with age in the skin of cheek, palm, and dorsum of foot, while remaining constant in neck and sole. In males, dermal thickness was significantly higher on the neck and dorsum of foot, while in females echo density of dermis was higher. The epidermal thickness was higher in males in all sites.

Table 2. Studies Reporting the Dermatological Applications of Ultra-High Frequency Ultrasound.

Author	Year	Application	Frequency
Liffers et al[13]	2003	Evaluation of normal skin and melanocytic lesions	50-100
Vogt et al[14]	2003	Study of skin and nails	100
Chen et al[15]	2004	Diagnosis of lichen sclerosus et atrophicus	30
Vogt et al[16]	2007	Evaluation of palmar skin and upper dermis	100
Chao et al[17]	2011	Skin characteristics associated to diabetic foot	55
Scola et al[18]	2011	Study of mid-dermal elastolysis	50
Guérin-Moreau et al[19]	2013	Description of pseudoxanthoma elasticum	20-50
Nassiri-Kashani et al[20]	2013	Preoperative evaluation of basal cell carcinoma	50
Rohrbach et al[21]	2014	Pre-operative evaluation of nonmelanoma skin cancer	35
Dybiec et al[22]	2015	Differential diagnosis of benign and malignant skin lesions	15-40
Berritto et al[23]	2016	Study of nail anatomy	70
Murray et al[24]	2016	Evaluation of localized scleroderma	35
Firooz et al[25]	2017	Skin epidermal and dermal thickness	50
Noe et al[26]	2017	Study of cutaneous sarcoidosis	40
Varkentin et al[27]	2017	Preoperative evaluation of melanocytic lesions	100
Tognetti et al[28]	2018	Skin lesions in Graves' disease	70
Tognetti et al[29]	2018	Study of cutaneous endometriosis	22-70
Wortsman et al[30]	2018	Evaluation of skin annexes	70
Naredo et al[31]	2019	Study of systemic sclerosis	50
Oranges et al[32]	2019	Evaluation of hidradenitis suppurativa	48-70
Reginelli et al[33]	2019	Preoperative evaluation of nodular skin melanoma	70
Oranges et al[34]	2020	Evaluation of cutaneous postradiation angiosarcoma	70

The Study of Skin Diseases

The studies retrieved from the literature report on a wide variety of pathologic conditions of the skin. Overall, 8 studies described cutaneous diseases,[15,18,19,24,26,29,31,32] 3 studies reported on cutaneous manifestations in course of systemic diseases,[17,28,34] and 7 studies described UHFUS aspect of malignant lesions.[13,16,20-22,27,33]

Chen et al[15] differentiated lichen sclerosus et atrophicus from morphea trough UHFUS examination, as the UHFUS finding of a hypoechoic band corresponding to the presence of severe lymphedema oriented the diagnosis. Scola et al[18] compared the aspect of mid-dermal elastolysis by means of both UHFUS and OCT, and found the presence of a decreased echogenicity in affected skin. Guérin-Moreau et al[19] described the UHFUS features of pseudoxanthoma elasticum, which consisted of undulating skin surface in absence of epidermis and dermal/epidermal interface alterations, and mid/deep dermis oval homogeneous hypoechogenic areas (papules) separated by normally echoic interpapular dermis. Murray et al[24] assessed the presence of epithelial modifications in course of scleroderma. The epithelial thickness slightly increased in correspondence with the active plaques compared with unaffected sites, while OCT was able to detect epithelial thickness variations also in inactive plaques. Noe et al[26] employed UHFUS to assess the granuloma burden in cutaneous sarcoidosis, and found a strong correlation with clinical severity score and histopathology. Tognetti et al[29] described the correlation between UHFUS and histology in the evaluation of cutaneous endometriosis. Endometriotic ectopic tissue–generated echoic posterior shadowing, while the irregular surface of the lesion appeared as a hyperechoic wavy epidermal band. Naredo et al[31] performed a texture analysis of UHFUS images of systemic sclerosis lesions, and were able to measure the thickness of the dermal layer separated from the hypodermal layer. Finally, Oranges et al[32] described the UHFUS findings in patients affected by hidradenitis suppurativa, which were characterized by the presence of fluid collections as nonhomogeneous hypoechoic oval lesions and widened hair follicles appearing as linear oblique hypoechoic structures.

Considering cutaneous manifestations in course of systemic diseases, Chao et al[17] evaluated the epidermal thickness and stiffness of plantar skin in patients with diabetic foot, finding increased values in diabetic patients compared with controls. Tognetti et al[28] investigated the UHFUS aspect of 2 extrathyroidal manifestations of Graves' disease, namely Graves' orbitopathy and pretibial myxedema. In both sites, glycosaminoglycans deposits were present in the reticular dermis and subcutaneous adipose tissue, appearing as moderately hyperechoic aggregates. UHFUS was also employed for post-UVA-1-phototherapy follow-up, allowing to assess the degree of reduction in the thickness of the dermal layers. Oranges et al[34] described a case of cutaneous postradiation angiosarcoma, where UHFUS revealed the malignant nature of the lesion, which appeared as an ill-defined inhomogeneous hypoechoic area, with multiple anechoic-reticulated channels.

The most relevant investigation conducted, however, is related to the early diagnosis of malignant skin lesions, in particular melanocytic lesions.[13,16,22,27,33] Liffers et al[13] described the UHFUS aspect of a malignant melanoma located in the subcutaneous fat, although entire visualization of the lesion was hindered by the reduced depth reached by the UHFUS beam. Similarly, Vogt et al[16] analyzed a malignant melanoma with UHFUS, which appeared as a hypoechoic structure in the hyperechoic dermis. However, in this case, the superficial localization of the lesion allowed to assess tumor depth and structure. Dybiec et al[22] applied UHFUS for the differential diagnosis between a benign cavernous hemangioma and a melanoma, retrieving different characteristics for the 2 lesions, which helped orient the diagnosis. Varkentin et al[27] compared the efficacy of UHFUS and OCT in imaging melanocytic lesions. UHFUS, although presenting slightly lower axial resolution compared with OCT, showed better image contrast and did not need any postprocessing following image acquisition. Depth of infiltration could be estimated employing both the techniques. Reginelli et al[33] described the UHFUS features of melanoma, which was characterized by oval or fusiform shape, inhomogeneity, hypoechogenicity, presence of smooth edges, and a variable degree of vascularization. In nodular melanomas, a regular hyperechoic band corresponding to the border between the lesion and the dermis was found. Interestingly, UHFUS measurement of tumor thickness and depth of invasion was reported to correlate with Breslow index, thus suggesting a role for UHFUS in the preoperative determination of the correct treatment.

Nassiri-Kashani et al[20] compared UHFUS-based measurements of basal cell carcinomas with pathology, in order to evaluate the effectiveness of presurgical assessment of tumor depth and width, finding moderate correlation between the 2 techniques. Similarly, Rohrbach et al[21] quantified tumor thickness in patients affected by basal cell carcinoma, and retrieved a good correlation value with histology, hypothesizing a role for UHFUS in surgery guidance, and therapy planning.

Insights Into a Role for UHFUS in Wound Assessment

As reported in the literature, UHFUS provides several advantages in the performance of clinical diagnosis in dermatology. In particular, the retrieval of the UHFUS features of a lesion, along with information on vascularization, contributes to integrate the data obtained with standard tests. In fact, the possibility to reliably assess the lesion's dimensions, width, and depth, and the relationship with surrounding anatomy appear of great importance not only for diagnosis but also for surgical planning. Moreover, the reduced invasiveness of UHFUS examination accounts for its repeatability over time, allowing to perform the follow-up of skin lesions in a noninvasive way, both in cases of conservative and surgical treatment. Interestingly, the possibility to perform texture analysis may also contribute to the performance of UHFUS diagnosis, thus highlighting potential variations in the echogenicity of a lesion even at an early stage.

At present, conventional US is frequently employed in diagnostic workup and therapeutic algorithm of lower extremities chronic wounds, in order to identify the presence of alterations in the truncal superficial and deep veins and arteries, and to determine whether they are associated to the presence of the lesion.[35] Clinical and instrumental evaluation with the calculation of the lesion's surface area[36-38] and the performance of the US assessment of the circulation in the affected area represent 2 fundamental steps in the diagnosis of chronic wounds. In particular, the assessment of the ankle brachial pressure index[39,40] is employed to give further indication for the performance of duplex ultrasound. In general, B-mode US and pulsed-wave Doppler are reported to be the most suitable diagnostic imaging tool for patients with lower extremities wounds. Moreover, US application in addition to standard compressive therapy and local wound care has been reported to improve ulcer healing and reduce the risk of recurrence, although its role is still debated.[41]

The use of high-frequency ultrasound has shown an interesting potentiality in chronic ulcers assessment, allowing the evaluation of tissue ultrastructure in lower leg ulcers, hypertrophic scars, keloids, and perilesional skin.[42] The measurement of echogenicity appears to correlate with skin tissue density, and it is mainly characterized by high echogenicity in the dermis compared with a relative hypoechogenicity of the subcutaneous fat. An increasing interest in high-frequency ultrasound has developed in pressure ulcers (PU) assessment with the evaluation of tissue density during early stage and development of PU.[43] This noninvasive technique was proposed as a monitoring test in order to prevent early skin deterioration in bedridden patients at risk for PU development.

From this perspective, UHFUS may prove beneficial in improving the management of wounds. The higher image resolution may help characterize the echostructural alterations associated with the development of the lesions, and could provide more precise dimensional assessment. Similarly, the UHFUS pulsed-wave Doppler evaluation may benefit from the increased anatomic detail, which could potentially allow the assessment of vascular structures of reduced dimensions, thus providing information also on microcirculation.

In the literature, some attempts to apply UHFUS to the study of ulcerative diseases have been reported with encouraging results.[32,34,44-46] For example, UHFUS allows to correctly stage and diagnose patients affected by hidradenitis suppurativa, and to decide the therapeutic approach.[32] In particular, a potential role in the monitoring following medical treatment and in the presurgical mapping appear feasible. Similarly, a report of a case of angiosarcoma highlighted the effectiveness of a combination between UHFUS and dermoscopy, and showed a good correlation between UHFUS and histology.[34] Interestingly, UHFUS has also been reported to be an effective diagnostic tool also in cases of mucocutaneous diseases involving the oral mucosa.[44-46] From this perspective, such an evaluation appears of great importance as it can provide a quantitative information on the lesion's echogenicity, thus allowing to better differentiate normal and affected tissue. It is also worth mentioning the effectiveness of texture analysis that can provide the retrieval of information on gray-scale distribution in a selected region of interest. In the future, we might speculate that a wider application of UHFUS in the study of mucocutaneous diseases may be of interest and of support in the diagnosis of complex clinical cases, where both skin and oral mucosa are affected.

Indeed, UHFUS-derived information appears extremely valuable in the assessment of wounds. While the role of conventional US is well established in the diagnosis of venous and arterial diseases, the diagnostic value of UHFUS in the evaluation of wounds has predominantly been investigated in terms of therapeutic approach.[11] However, considering previous experience, we might speculate that UHFUS could become an integration to the clinical assessment of wounds, as it may overcome the limits related to the clinical assessment of the lesions in terms of dimensions and depth. Moreover, adjunctive data on vascularization may be provided by Doppler UHFUS, and thus integrate conventional diagnostic workup. Data deriving from UHFUS may also contribute to the decisional process behind the choice of different treatment options, and provide a valuable support in the follow-up of ulcerative skin lesions. We must recognize, however, that despite the relatively common use of ultrasonography in dermatology, UHFUS presents its own semeiotic and provides a "magnified" view of the structures commonly explored with conventional US. From this perspective, training has a pivotal role in the performance of UHFUS examination, and the presence of a learning curve is undeniable. Nonetheless, UHFUS application to the assessment of wounds appears promising, and requires further evaluation.

Conclusions

In the attempt to reduce the invasiveness of the diagnostic workup of skin lesions, the application of UHFUS appears to have all the characteristics to become a routinely used tool for the evaluation of skin lesions. In fact, the possibility to achieve higher image resolution compared with conventional ultrasonography, along with the scarce invasiveness and repeatability of the technique, make UHFUS suitable for the investigation of the majority of skin lesions. Overall, UHFUS appears to be the next generation in ultrasound imaging in dermatology, and holds the promise to become an integrative tool in the diagnosis, treatment, and follow-up of wounds.

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